CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20939

ADMINISTRATIVE DOCUMENTS

JAN 2 8 2000

RHPM Review of Final Printed Labeling

Application:	NDA 20-939 Diltiazem Hydrochloride Extended-release Capsules
Applicant:	Biovail Laboratories Incorporated
Letter Date:	January 4, 2000
Stamp Date:	January 5, 2000

Background

An approvable letter was issued for NDA 20-939 on December 10, 1999. The applicant was asked to submit final printed labeling identical to the draft text enclosed in the letter. The applicant complied with this request by submitted final printed labeling in a submission dated January 4, 2000.

Review

The final printed labeling is identical to the approvable draft labeling with the following exceptions:

1) In the third sentence of the **CLINICAL PHARMACOLOGY: Diltiazem Hydrochloride Extended-release Capsules** subsection should have been deleted.

2) In the first sentence of the second paragraph under **PRECAUTIONS: Drug Interactions**, a comma should be inserted after "As with all drugs."

3) In the second sentence under **PRECAUTIONS: Drug interactions/Benzodiazepines**, the word should be replaced with "increased."

4) In the second paragraph under **ADVERSE REACTIONS**, the words should be deleted.

5) Under **HOW SUPPLIED**, the **Manufacturing Statement** has been replaced with the following:

Recommendation

I spoke with Mr. Wayne Kreppner of Biovail on January 20, 2000, and he agreed to correct the mistakes listed in items 1, 2, 3 and 4 above at the time of their next printing. The change in number 5 is acceptable. An approval letter will be drafted for Dr. Lipicky's signature.

/S/

David Roeder
Regulatory Health Project Manager

dr/1-13-00
cc: NDA 20-939
HFD-110

RHPM Package Overview #3

Application: NDA 20-939
Diltiazem Sustained Release Capsules

Applicant: Biovail Laboratories Incorporated

Indication: Hypertension

Primary Goal Date: December 10, 1999

Secondary Goal Date: February 10, 2000

Background

NDA 20-939 provides for the use of a once-daily formulation of diltiazem for the treatment of hypertension. Biovail also has an ANDA for the same product (ANDA 75-116). They submitted NDA 20-939 to our division as a 505(b)(1) NDA because their ANDA was being blocked by marketing exclusivity.

NDA 20-939 was originally submitted on November 7, 1997 (stamp date: November 5, 1997). They did one clinical study in hypertension patients. We refused to file the application because the firm did not have a valid right of reference to the pharmacology/toxicology data.

This application was discussed at a CDER Refuse to File Review Committee Meeting on February 10, 1999. At that meeting, the sponsor was informed that they have the right to have the application filed over protest. The application could then undergo FDA review while the Biovail worked on obtaining a right of reference to the pharmacology/toxicology data. Since this filing over protest did not follow the timelines or procedures described in 21 CFR 314.101(a)(3) the start date for the user fee clock was determined to be the date of the CDER Refuse to File Review Committee Meeting on February 10, 1999.

Biovail submitted letters from Watson Laboratories authorizing the FDA to refer to all human and animal pharmacology and toxicology data from NDA 20-092. The letters, however, authorized the use of these data in support of "any New Drug Application (NDA) filed by Biovail Corporation International ... for an extended release oral dosage formulation of diltiazem ..." Biovail Corporation International (BCI) is not the sponsor of this NDA. Biovail Laboratories Incorporated (BLI), which is a wholly owned subsidiary of BCI, is the sponsor. Per a request from our General Counsel, BCI submitted a letter dated October 26, 1999 explaining the corporate relationship between BCI abnd BLI and authorizing the use of the rights of reference to support approval of NDA 20-939.

Chemistry

Reviewer: Ram Mittal, Ph.D.

The reviewer recommends approval pending satisfactory completion of the facility inspection.

Facility Inspection: Acceptable

Labeling and Nomenclature: The sponsor has not proposed a trade name.

Dissolution specifications: The biopharmaceutics reviewer has recommended revised dissolution specifications. These recommendations will be included in the approvable letter.

Pharmacology

Reviewer: Chuck Resnick, Ph.D.

Dr. Resnick has recommended labeling changes.

Biopharmaceutics/Clinical Pharmacology

Reviewer: Tom Parmelee, PharmD

The biopharm/clin pharm reviewer has recommended labeling changes. The recommended changes regarding tacrolimus, buspirone and quinidine have not yet been incorporated into the other diltiazem labeling. Dr. Lipicky recommended that we wait until after this NDA is approved and request the additional changes to all diltiazem products at once.

Dr. Parmalee has also recommended revised dissolution specifications that will be included in the approvable letter.

Statistical

Reviewer: Lu Cui, Ph.D.

Dr. Cui will provided statistical analyses for Dr. Chen's secondary medical review.

Clinical

Reviewer: Cristobol Duarte, M.D.

Dr. Duarte recommends approval of the application.

DSI

A DSI audit is not necessary.

Pediatric

The Pediatric Rule does not apply to this application since it is not a new formulation

David Roeder
Regulatory Health Project Manager

dr/10-12-99/11-29-99/12-8-99

cc: NDA 20-939
HFD-110
HFD-110/DRoeder

RHPM Package Overview #2

Application:	NDA 20-939 Diltiazem Sustained Release Capsules
Applicant:	Biovail Laboratories Incorporated
Indication:	Hypertension
Primary Goal Date:	December 10, 1999
Secondary Goal Date:	February 10, 2000

Background

NDA 20-939 provides for the use of a once-daily formulation of diltiazem for the treatment of hypertension. Biovail also has an ANDA for the same product (ANDA 75-116). They submitted NDA 20-939 to our division as a 505(b)(1) NDA because their ANDA was being blocked by marketing exclusivity.

NDA 20-939 was originally submitted on November 7, 1997 (stamp date: November 5, 1997). They did one clinical study in hypertension patients. We refused to file the application because the firm did not have a valid right of reference to the pharmacology/toxicology data.

This application was discussed at a CDER Refuse to File Review Committee Meeting on February 10, 1999. At that meeting, the sponsor was informed that they have the right to have the application filed over protest. The application could then undergo FDA review while the Biovail worked on obtaining a right of reference to the pharmacology/toxicology data. Since this filing over protest did not follow the timelines or procedures described in 21 CFR 314.101(a)(3) the start date for the user fee clock was determined to be the date of the CDER Refuse to File Review Committee Meeting on February 10, 1999.

Biovail submitted letters from Watson Laboratories authorizing the FDA to refer to all human and animal pharmacology and toxicology data from NDA 20-092. The letters, however, authorized the use of these data in support of "any New Drug Application (NDA) filed by Biovail Corporation International ... for an extended release oral dosage formulation of diltiazem ..." Biovail Corporation International (BCI) is not the sponsor of this NDA. Biovail Laboratories Incorporated (BLI), which is a wholly owned subsidiary of BCI, is the sponsor. Per a request from our General Counsel, BCI submitted a letter dated October 26, 1999 explaining the corporate relationship between BCI abnd BLI and authorizing the use of the rights of reference to support approval of NDA 20-939.

Chemistry

Reviewer: Ram Mittal, Ph.D.

Review in draft. The reviewer recommends approval pending satisfactory completion of the facility inspection.

Facility Inspection: The inspection of the has been performed, but the report has not been generated.

Labeling and Nomenclature: The sponsor has not proposed a trade name.

Dissolution specifications: The biopharmaceutics reviewer has recommended dissolution specifications different from those approved with ANDA 75-116. This issue should be resovled prior to approval.

Pharmacology

Reviewer: Chuck Resnick, Ph.D.

Dr. Resnick has recommended labeling changes.

Biopharmaceutics/Clinical Pharmacology

Reviewer: Tom Parmelee, PharmD

The biopharm/clin pharm reviewer has recommended labeling changes. He has also recommended revised dissolution specifications that differ from those approved with ANDA 75-116.

Statistical

Reviewer: Lu Cui, Ph.D.

Dr. Cui will provided statistical analyses for Dr. Chen's secondary medical review.

Clinical

Reviewer: Cristobol Duarte, M.D.

Dr. Duarte recommends approval of the application.

DSI

A DSI audit is not necessary.

/S/

David Roeder
Regulatory Health Project Manager

df/10-12-99/11-29-99

cc: NDA 20-939
HFD-110
HFD-110/DRoeder

DEC 10 1999

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION — **Public Health Service**

Division or Cardio-Renal Drug Products — **Memorandum**

Date : 12/10/99

From : Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

Subject : Approvable, NDA 20-939, diltiazem extended release, Biovail

To : File

The approval of NDA 20-939 is based upon the submitted clinical trial reviewed by Dr. Duarte. This was a parallel group, double-blind placebo-controlled comparison of 4 doses of diltiazem extended release (doses of 120, 180, 300 and 540 mg, once daily). The study found clear dose-related antihypertensive effects of this formulation of diltiazem, with a maximum group average decrease of –8.6 mm Hg for the 540 mg arm. Of course, this is not surprising since diltiazem has been on the market as an antihypertensive for years. This single trial is sufficient as a basis of approval.

This NDA is also supported by animal toxicology data that is owned by Watson and to which Biovail has right-- reference. The adequacy of the data is supported by Dr. Resnik's review.

Dr. Mittal has reviewed the manufacturing and controls information and has found it to be acceptable. On site inspections have also been acceptable.

The biopharmaceutics requirements have been found acceptable in the review by Dr. Parmelee.

The administrative history of this NDA is long an complicated. Suffice it to say here that I am familiar with history and am satisfied that we can approve this NDA.

cc: NDA 20-939
HFD-110
HFD-110/DReeder

D. Roeder
NOV 24 1999

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 11/24/99
From: Shaw T. Chen, M.D., Medical Team Leader, HFD-110
To: Director, Division of Cardiorenal Drug Products, HFD-110

Subject: NDA 20-939, Diltiazem ER for Hypertension, Approvability

OVERVIEW

This memorandum and the attached material constitute the Division's recommendation that NDA 20-939, diltiazem ER for hypertension, be approved.

This is an application for a new sustained release formulation of a well-known calcium channel blocker, diltiazem, to be used in the same indications as that approved previously for different formulations. As concluded in the relevant reviews, critical biopharmaceutical issues with the new dosage forms have been adequately addressed and the clinical studies were all of proper design and execution. All regulatory reviews have been completed as the date of this memo and there are no unresolved problems that may affect the recommended action.

Pharmacokinetically, diltiazem has an extensive first pass metabolism and a short serum half life, thus requires multiple daily dosing. There are five different sustained release formulations of diltiazem approved for hypertension, four of which are once-daily regimens.

There are no surprising findings in either efficacy or safety of this formulation and the application is ready for approval.

BIOPHARMACEUTICS

As summarized in Dr. Parmelee's clinical pharmacology/biopharmaceutics review, the new diltiazem ER formulation has been adequately tested. The findings are re-iterated as follows:

i) Administered under fed/fasting and single/multiple dosing, it was found to be bio-equivalent to the approved product Cardizem CD.
ii) Bioavailability of diltiazem and its active metabolites increase slightly more than dose-proportionality.
iii) Since there was no apparent dose-dumping, diltiazem ER can be taken regardless of food.
iv) Diltiazem was detected 2 hrs after dosing of ER formulation, reach maximum level of 146 ng/ml at about 13 hrs, and had a half life of 7 hrs.
v) While the method for dissolution test was acceptable, the reviewer recommended a different set of specification (see page 5 of the biopharm review).
vi) Bioequivalence between clinical trial batch and those to be marketed after approval was tested for the 300 mg dose. Waiver for testing other doses for bioequivalence was considered reasonable by the reviewer.

The biopharm reviewer's comments related to drug interactions (with quinidine, buspirone and tacrolimus) on the draft labeling are all appropriate and have been incorporated into the marked-up copy.

EFFICACY FOR HYPERTENSION

Diltiazem-ER was evaluated in a double-blind, randomized, parallel placebo-controlled, studies with total of 266 patients with mild to moderate hypertension. Patients were randomized to placebo, or diltiazem ER at 120, 180, 300,540 mgs (51-54 patients per group). After 1 week titration, patients were treated for total of 8 weeks.

The primary efficacy endpoint in each of these studies was the change in diastolic blood pressure (DBP) from baseline at the end of dosing interval. Treatment effects on systolic blood pressures, in standing position, and response rate were secondary analyses.

Overall discontinuation was 14% in the diltiazem groups (7-19%) and 20% in the placebo group. With the last observed values carried forward as endpoint, the sponsor listed 258 (97% of randomized) for the primary "intent-to-treat" analyses. The data in the following table demonstrate that diltiazem-ER, at 120-540 mg qd, is a significantly more effective antihypertensive agent than placebo, with an overall ANOVA p value of 0.0001. At this dose range, the placebo-subtracted net decreases in supine diastolic BP at trough were dose-related, with a p value of 0.0001 for the slope.

Least square mean reduction in supine DBP*

	Diltiazem ER in mg qd						
in mmHg	placebo	120	180	300	540	p (overall)	p (slope)
diastolic	2.6	1.9	5.4	6.1	8.6	0.0001	0.0001
systolic	1.4	-1.2	6.1	6.7	10.0	0.0008	0.0002

[ ] are significantly different from placebo

* Dr. Lu Cui's analyses

The above table also shows a very similar effect on the systolic BPs.

The **percentages of responders** (SDBP reduction of $\geq$ 10 mmHg or to $\leq$ 90 mmHg at trough) also increased with dose (Table below). The response rates for 180-540 mg/day were in the range of 15-25% more than that of placebo. The response rate was not different from placebo for the low dose of 120 mg.

Response rates	Diltiazem ER in mg qd				
	placebo	120	180	300	540
% of Patients	26	24	41	45	51

Although ABPM measurement was planned in the protocol, no data were presented in the application. Upon the medical reviewer's inquiry, the sponsor claimed that no ABPM was collected.

At the dosages studied, the peak effects were not excessive (trough/peak ratios were 0.8-1.2 at 120-540 mg, see Table 17 of Medical Review). The maximal effects corresponded approximately to the plasma diltiazem concentrations, especially the diastolic BPs (Table 16 of Medical Review). Blood pressure reduction appeared to reach maximal effect in 1-2 weeks (see Tables 10 and 12 of Medical Review)

Overall responses to diltiazem-ER were probably not dependent on patients age, gender, race, baseline blood pressures. Sample sizes were too small for subgroup analyses of individual doses.

SAFETY IN HYPERTENSION

Diltiazem-ER appeared to be safe and well-tolerated as an antihypertensive treatment. There were no qualitative or quantitative surprises in safety experiences of this new formulation, as compared with known effects of previously approved dosage forms. Since this is a new formulation and did not require evaluation as extensive as new molecular entity, rare but more serious events would not be detectable in the relatively limited safety database of 266 patients. The safety sections of the labeling for diltiazem-ER should therefore rely on the previous experience with other dosage forms.

As noted in the hypertension trial described above for efficacy, 215 of 266 patients received diltiazem-ER. The patient numbers were evenly distributed over dosages of 120-540 mg, and a great majority were treated for 8 weeks (86%). Overall **discontinuation** due to adverse events were rare and not different from placebo (4% in both, see Table 3 of Medical Review), but appeared to be more frequent in the higher dose groups (from 0 at 120 mg to 9% for 540 mg, ibid). Specific causes for the 11 withdrawals were listed in Dr. Duarte's medical review (Table 6).

About half all treatment groups reported **adverse events**, no substantial between group differences were noted during the randomized treatment period. Most commonly seen were headache, pharyngitis, edema, pain and infections. Neither the total adverse experience nor individual incidences were clearly dose-related in this small database.

There were no new findings in ECG or routine laboratory tests in the controlled trial of ER dosage forms. The numbers of individual events were too small to shed any additional light and warning or precaution of previously approved labeling should be retained.

As noted above, there was no excessive reduction of blood pressure at peak effect of the drug, with acceptable trough to peak ratios. Clinically significant **hypotension** and other related adverse experiences in diltiazem-ER treated patients were not common and did not result in withdrawal. Precautionary notes about heart failure should be included, however, as for other formulation of diltiazem.

Significant **bradycardia** reported as adverse events in the diltiazem-ER hypertension study was not more frequent than that in the current labeling for other formulations. However, there was a dose related decrease in heart rate (by mean of 3-6 bpm at 300-540 mg, see Table 13 of Medical Review) in this study.

OVERALL ASSESSMENT

The clinical study of diltiazem-ER for hypertension was well-designed and the reviewers did not find any serious deficiency in study execution. The results were easily interpretable and the conclusions do support the efficacy claims for the new formulation.

There were no surprises in safety experiences in the use of diltiazem-ER and the biopharmaceutics of the new sustained release formulation has been adequately characterized.

While detailed labeling may have to rely on previous experiences with other dosage forms of this well-known calcium channel blocker, there is sufficient information to serve as the basis for approval for diltiazem ER.

PEDIATRIC/GERIATRIC/FEMALE USE

There are no clinical trials assessing the efficacy or safety of diltiazem-ER in pediatric patients, either completed or in progress. The sponsor claimed that the drug has little potential for use in children and thus did not commit to any study in children with hypertension.

Efficacy and safety of diltiazem-ER as treatment for hypertension in the elderly (65 year and older), female and non-Caucasian patients cannot be assessed from the small clinical database. For this well-studied drug, there is no reason not to borrow the subgroup experiences from other similar and different formulations for labeling.

DRAFT LABELING

The draft labeling submitted by the sponsor has been edited. Comments by Dr. Resnick on pre-clinical data and by Dr. Parmelee on biopharmaceutical section have been incorporated into the draft labeling

CONCLUSIONS

Diltiazem-ER appeared to be an effective and safe treatment for hypertension. It is recommended that diltiazem-ER be approved with the edited draft labeling.

/S/

Shaw T. Chen, M.D.,Ph.D.

cc:
ORIG: NDA- 20-939
HFD-110
HFD-110/Roeder/Duarte
HFD-710/Cui
HFD-860/Parmelee
HFD-110/SChen/11/24/99

SECTION 13 – PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

List of Patents

The Diltiazem Hydrochloride Extended-release Capsules, USP formulation is covered by two (2) patents:

- Extended-release form of diltiazem
  Arthur M. Deboeck, Phillippe R. Baudier
  US Patent number: 5,288,505 February 22, 1994.

- Extended-release form of diltiazem
  Arthur M. Deboeck, Phillippe R. Baudier
  US Patent number: 5,529,791 June 25, 1996.

A copy of both patents is enclosed.

SECTION 14 – PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Certification

This section is not applicable to this New Drug Application.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20939	**Trade Name:**	DILTIAZEM HCL ER CAPS 120/180/240/300MG
Supplement Number:	-	**Generic Name:**	DILTIAZEM HCL ER CAPS 120/180/240/300MG
Supplement Type:		**Dosage Form:**	EXC
Regulatory Action:	AE	**Proposed Indication:**	hyertension

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
The pediatric rule does not apply to this NDA because this formulation of diltiazem has already been approved (12-8-99)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DAVID ROEDER

/S/ 12-8-99
Signature Date

BIOVAIL
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BIOVAIL
BIOVAIL

DEBARMENT CERTIFICATION

Diltiazem Hydrochloride Extended-release Capsules 120 mg, 180 mg, 240 mg and 300 mg

In accordance with the requirement of section 306 (k) of the Federal Food, Drug and Cosmetic Act, I, the undersigned, certify that Biovail Laboratories Incorporated did not use any person debarred under subsection (a) or (b) of 306 (k) in any capacity in connection with this application, nor will Biovail Laboratories Incorporated use any such person in connection with this application.

Furthermore, I certify that neither the applicant nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of section 306.

Eugene Melnyk
President
BIOVAIL LABORATORIES INCORPORATED

Oct 18/99
Date

BIOVAIL LABORATORIES INCORPORATED
HELSTON PARK, BUILDING 2, COLLYMORE ROCK, ST. MICHAEL, BH1, BARBADOS, W.I. • TEL (246) 437-7080 FAX (246) 437-7085

FEB 10 1999

Memorandum to the File

Date: February 10, 1999

Application: NDA 20-939
Diltiazem Hydrochloride Capsules

Applicant: Biovail Laboratories, Inc.

Subject: File Over Protest

A CDER Refusal-to-File meeting was held on February 10, 1999 in which the case of NDA 20-939 was discussed. The applicant was in attendance for part of the meeting. Biovail was informed at the meeting that they could file this application over protest if they so wished. The date of this meeting will be considered the "informal conference" described in 21 CFR 314.101(a)(3). This date will also be considered to be the start of the user fee clock.

/S/

David Roeder
Regulatory Health Project Manager

cc: NDA 20-939
HFD-110
HFD-110/DRoeder

D. Roeder

JAN 12 1999

Memorandum to the File

Date: January 11, 1999

Application: NDA 20-939
Diltiazem HCl Extended Release Capsules

Sponsor: Biovail Laboratories Incorporated

We initially refused to file NDA 20-939 for two reasons:

1) The applicant did not have a valid right of reference for the preclinical safety data.

2) Biovail currently had a pending ANDA for the same product, and we could not accept two applications for the same product from the same applicant.

Prior to issuing the refusal to file letter on January 13, 1998, we had received advice from our General Counsel that 21 CFR 314.101(d)(8)(i) could be used as a basis for refusing to file an NDA for a product that is covered by another pending application from the same applicant. This was consistent with the approach taken by the Office of Generic Drugs when one applicant submits two ANDAs for the same product. After issuing the letter, however, Biovail complained to our General Counsel about our interpretation of that regulation. We were advised by General Counsel to issue an amended refusal to file letter in which the second deficiency was deleted. This was done on March 27, 1998.

/S/

David Roeder
Regulatory Health Project Manager

dr/1-12-99

cc: NDA 20-939
HFD-110
HFD-110/DRoeder

Roeder

JAN 26 1998

Minutes of a Meeting

Date: December 17, 1998

Application: NDA 20-939
Diltiazem HCl Extended Release Capsules

Sponsor: Biovail Laboratories

Subject: Filing

Participants

FDA

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
Charles Ganley, M.D., HFD-110, Medical Team Leader
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
David Roeder, HFD-110, Project Manager
Kun Jin, Ph.D., HFD-710, Statistician
Patrick Marroum, Ph.D., HFD-860, Biopharmaceutics Team Leader

Background

Biovail currently has an approved NDA for a once-daily extended release diltiazem capsule (NDA 20-401). NDA 20-939 provides for a revised formulation that is intended to be bioequivalent to Cardizem CD. The NDA contains one clinical trial.

The sponsor is relying on a right of reference that was originally granted by Hoechst Marion Roussel (HMR) to support the approval of Biovail's NDA 20-401. HMR had informed us, however, that their right of reference would not cover any formulation that had not been originally submitted to NDA 20-401. This was conveyed to Biovail in our letter of November 8, 1996.

Biovail currently has a pending ANDA for the same product.

Reviewers

Chemistry:	Kathleen Jongedyk
Pharmacology:	Charles Resnick, Ph.D.
Biopharmaceutics:	Patrick Marroum, Ph.D.
Statistics:	Kun Jin, Ph.D.
Clinical:	Sughok Chun, M.D.

Meeting

None of the review disciplines found any reason to refuse to file the application. Mr. Roeder,

however, raised the following two issues:

1) The sponsor does not have a valid right of reference for the pharmacology/toxicology data. Since NDA 20-939 does not contain these data, it is not a complete application and should therefore not be filed.

2) The applicant, Biovail Laboratories, has a currently pending ANDA. It is the policy of the Agency not to accept duplicate applications from the same sponsor for the same product. NDA 20-939 should therefore not be filed.

Dr. Lipicky agreed that the application should not be filed.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Raymond Lipicky, M.D.

dr/1-10-98/1-26-98

RD: PMarroum/1-15-98
KJin/1-15-98
CGanley/1-15-98
NAMorgenstern/1-20-98

cc: NDA 20-939
~~HFD-110~~
HFD-110/CSO